Amberlyst-A21 as a New and Efficient Surface Catalyst for the Conjugate Addition of Nitroalkanes to Methyl Acrylate: An Improved Synthesis of Methyl 4-Nitro- and 4-Oxoalkanoates

Roberto Ballini,*[a] Marino Petrini,[a] Goffredo Rosini*[b]

[a] Dipartimento di Scienze Chimiche, Università, Via S. Agostino, 1, I-62032 Camerino, Italy

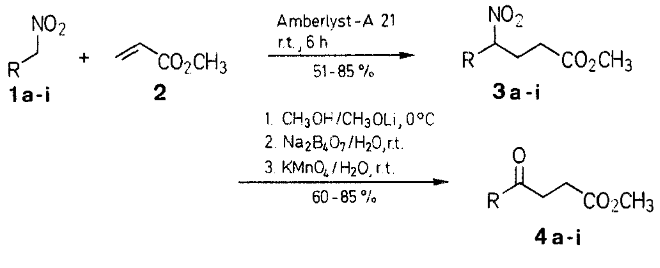
[b] Istituto di Chimica Organica, Università, V. le Risorgimento, 4, I-40136 Bologna, Italy

Utilization of Amberlyst-A21 without solvent in the conjugate addition of nitroalkenes to methyl acrylate, affords 4-nitroalkanoic methyl esters in good yields. Successive Nef reaction, using potassium permanganate, provides functionalized 4-oxoalkanoic methyl esters.

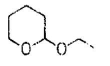
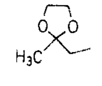
Aliphatic nitro compounds occupy a crucial position on the interconversion of organic functional groups. However, for any class of compounds to have broad synthetic utility it must amenable to *C*–*C* bond-forming processes.[1] For this purpose, aliphatic nitro compounds appear to be especially attractive. Michael additions of nitroalkanes are important reactions in organic synthesis and have been studied extensively. They are typically run with homogeneous solution of the reactants in organic solvents using soluble bases.[2–14]

Recentely we reported an improved method for conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds, on alumina surface in the absence of a solvent.[15,16] In connection with our interest in the synthesis of methyl 4-oxoalkanoates which are useful synthetic intermediates for γ-lactones, butenolides, cyclopentenones, and heterocyclic compounds,[17] we tried to use basic alumina for the conjugate addition of nitroalkanes to methylacrylic esters, which are poor electrophiles; the yields were unsatisfactory. We now report the utilization of Amberlyst-A21 (from Carlo Erba S.p.A.)[18] as new and efficient surface catalyst for the conjugate addition of nitroalkanes to methyl acrylate.

Primary nitroalkanes **1a–i** undergo Michael addition with methyl acrylate (**2**) on Amberlyst-A21 surface, in the absence of a solvent, to give the 4-nitroalkanoic esters **3a–i**, useful intermediates in organic synthesis,[19] in good yields. This procedure works well on a gram scale and good results are also obtained with acid- or base-sensitive substrates. Successive Nef reaction of the 4-nitroalkanoic esters **3a–i**, using potassium permanganate,[20] furnishes functionalized 4-oxoalkanoic esters **4a–i** in good yields (Scheme **A**).

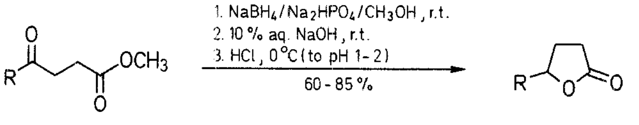


1a-i **2** **3a-i** **4a-i**

3, 4	R	3, 4	R
a	CH_3	**g**	$CH_3OCO(CH_2)_4$–
b	n-C_4H_9	**h**	$C_2H_5CO(CH_2)_2$
c	n-C_5H_{11}		
d	C_6H_5		
e	p-$CH_3C_6H_4CH_2$	**i**	
f			

Scheme A

As an application of our method, we report here the lactonization of the 4-oxoalkanoicesters **4c** and **4d** by reduction with sodium borohydride (Scheme **B**), to afford 4-nonanolide (**5c**), a famous perfume, the so-called aldehyde C-18, and 4-phenyl-4-butanolide γ-phenyl-γ-butyrolactone, **5d**, which shows important biological activities.[21]



4c,d

5c R = n-C_5H_{11}
d R = C_6H_5

Scheme B

Table 1. Methyl 4-Nitroalkanoates **3** Prepared

3	Yield[a] (%)	b.p.[b] (°C/Torr)	Molecular Formula[c]	IR (cm^{-1})[d] C=O	IR (cm^{-1})[d] NO_2	^{1}H-NMR ($CDCl_3$)[e] δ, *J* (Hz)
a	76	130/0.1	$C_6H_{11}NO_4$ (161.2)	1735	1545	1.55 (d, 3H, *J* = 6.5); 2.00–2.50 (m, 4H); 3.70 (s, 3H); 4.35–4.80 (m, 1H)
b	77	150/0.5	$C_9H_{17}NO_4$ (203.2)	1735	1545	0.9 (t, 3H, *J* = 6.0); 1.1–2.55 (m, 10H); 3.7 (s, 3H); 4.4–4.8 (m, 1H)
c	80	165/0.2	$C_{10}H_{19}NO_4$ (217.3)	1740	1545	0.9 (t, 3H, *J* = 6); 1.1–2.5 (m, 12H); 3.7 (s, 3H); 4.3–4.75 (m, 1H)
d	78	205/0.4	$C_{11}H_{13}NO_4$ (223.2)	1735	1545	2.18–3.00 (m, 4H); 3.68 (s, 3H); 5.45–5.72 (m, 1H), 7.25–7.63 (m, 5H)
e	80	oil[f]	$C_{13}H_{17}NO_4$ (251.3)	1735	1545	1.95–2.55 (m, 4H); 2.3 (s, 3H); 2.8–3.4 (m, 2H); 3.65 (s, 3H); 4.55–4.95 (m, 1H); 7.1 (s, 4H)
f	85	205/0.3	$C_{10}H_{17}NO_4$ (215.2)	1735	1550	1.32 (s, 3H); 1.8–2.9 (m, 6H); 3.68 (s, 3H); 3.95 (s, 4H); 4.6–4.9 (m, 1H)
g	83	oil[f]	$C_{11}H_{19}NO_6$ (261.2)	1735	1550	1.1–2.65 (m, 12H); 3.68 (s, 6H); 4.35–4.80 (m, 1H)
h	70	235/0.4	$C_{10}H_{17}NO_5$ (231.2)	1735 1715	1545	1.2 (t, 3H, *J* = 7.5); 1.85–2.70 (m, 10H); 3.68 (s, 3H); 4.4–4.8 (m, 1H)
i	51	240/0.5	$C_{11}H_{19}NO_6$ (261.3)	1735	1550	1.32–1.92 (m, 6H); 2.00–2.60 (m, 4H); 3.30–4.35 (m, 4H); 3.70 (s, 3H); 4.48–5.00 (m, 2H)

[a] Yield of isolated pure product.
[b] Determined by Kugelrohr distillation.
[c] Microanalyses were performed using a C, H, N Analyzer Model 185, Hewlett-Packard Co.; C ±0.22, H ±0.18, N ±0.24.
[d] Recorded on a Perkin-Elmer 297 spectrometer.
[e] Recorded at 90 MHz using a Varian EM 390 spectrometer.
[f] Purified by chromatography over Silica gel (0.063–0.200 mm) with EtOAc/hexane (2:8) as eluent.

Table 2. Methyl 4-Oxoalkanoates **4** Prepared.

4	Yield[a] (%)	b.p.[b] (°C/Torr)	Molecular Formula[c]	IR (cm^{-1})[d] $C=O_{ester}$	IR (cm^{-1})[d] $C=O_{ketone}$	^{1}H-NMR ($CDCl_3$)[e] δ, *J* (Hz)
a	60	160/0.2	$C_6H_{10}O_3$ (130.1)	1735	1718	2.2 (s, 3H); 2.5–2.9 (m, 4H); 3.68 (s, 3H)
b	82	115/0.3	$C_9H_{16}O_3$ (172.2)	1735	1715	0.9 (t, 3H, *J* = 6.75); 1.1–1.82 (m, 4H); 2.32–2.90 (m, 6H); 3.68 (s, 3H)
c	79	121/0.2	$C_{10}H_{18}O_3$ (186.2)	1735	1715	0.85 (t, 3H, *J* = 6) 1.00–1.80 (m, 6H); 2.3–2.85 (m, 6H); 3.65 (m, 3H)
d	66	190/0.5	$C_{11}H_{12}O_3$ (192.2)	1735	1685	2.78 (t, 2H, *J* = 6.75); 3.32 (t, 2H, *J* = 6.75); 3.70 (s, 3H); 7.18–7.75 (m, 3H); 7.83–8.19 (m, 2H)
e	70	oil	$C_{13}H_{16}O_3$ (220.3)	1730	1715	2.31 (s, 3H); 2.40–2.90 (m, 4H); 3.62 (s, 3H); 3.67 (s, 2H); 7.13 (s, 4H)
f	80	175/0.4	$C_{10}H_{16}O_5$ (216.2)	1735	1715	1.4 (s, 3H); 2.3–3.0 (m, 4H); 2.8 (s, 2H); 3.68 (s, 3H); 3.98 (s, 4H)
g	77	215/0.1	$C_{11}H_{18}O_4$ (214.25)	1735	1715	1.4–1.8 (m, 4H); 2.12–2.88 (m, 8H); 3.68 (s, 6H)
h	85	170/0.1	$C_{10}H_{16}O_4$ (200.2)	1735	1710	1.05 (t, 3H, *J* = 7.5); 2.15–3.95 (m, 10H); 3.68 (s, 3H)
i	65	190/0.3	$C_{11}H_{18}O_5$ (230.25)	1735	1718	1.31–2.04 (m, 6H); 2.50–3.00 (m, 4H); 3.68 (m + s, 5H); 4.13–4.40 (m, 2H); 4.55–4.75 (m, 1H)

[a] Yield of isolated product pure, at least 94% pure by GLC.
[b, d, e] see Table 1.
[c] Microanalyses were performed using a C, H, N Analyzer Model 185, Hewelett-Packard Co.; C ±0.20, H ±0.19.

In summary, the mild reaction conditions, the simple work-up, the short reaction times, and the good yields make Amberlyst-A21 a convenient catalyst for the synthesis of polyfunctional 4-nitroalkanoic esters on a large scale.

Microanalyses were performed by using a C, H, N Analyzer Model 185 from Hewlett-Packard Co. GLC analyses were performed on a Carlo Erba Fractovap 4160; Column: OV1 duran glass, 25 × 0.3 mm; film thickness 0.4–0.45 μm; injector temperature: 300 °C; detector flame ionization: 300 °C; carrier: nitrogen at 3 mL/min.; column temperature: 65 °C; programme: 3 min at 65 °C, then from 65 °C to 300 °C at 15 °C/min and held. IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer. ^{1}H-NMR spectra were recorded at 90 MHz on a Varian EM 390.

Methyl 4-Nitroalkanoates 3a–i; General Procedure:
To stirred nitro compound **1** (0.036 mol), cooled with an ice/water bath, is added methyl acrylate **(2)**; 3.1 g, 0.036 mol) and stirring is continued for 5 min. Amberlyst-A21 (20 g) is then added and stirring is continued for 6 h at room temperature. The resultant mixture is extracted with Et_2O (3 × 40 mL), the extract is evaporated, and the residue is purified by distillation or chromatography over silica gel (0.063–0.200 mm) with ethylacetate/hexane (2:8) as eluent to give the pure compounds **3**.

Methyl 4-Oxoalkanoates 4a–i; General Procedure:
To a stirred solution of the respective ester **3** (8 mmol) in methanol (10 mL) 0–2 °C under argon is added dropwise, over a period of 10 mi, a freshly prepared methanolic solution (30 mL) of lithium methoxide (from 59 mg Li, 8.4 mmol). The solution is stirred for 15 min, treated with 5% aqueous $Na_2B_4O_7$ solution (30 mL) at pH = 9, then potassium permanganate (1.33 g, 8.8 mmol) in 5% aqueous $Na_2B_4O_7$ solution (30 mL) is added, and stirring is continued for 30 min at room temperature. The solution is filtered, treated with aqueous $NaHSO_3$ (the solution discolorates), and extracted with $CHCl_3$ (3 × 50 mL). The organic layer is dried (Na_2SO_4) and evaporated to afford compound **4** (at least 94% pure by GLC).

Reductive Cyclization of 4-Oxoalkanoic Esters 4c, d to 4-Alkanolides 5c, d; General Procedure:

To a mixed solution of $NaBH_4$ (0.1 g, 2.6 mmol) and $Na_2HPO_4 \cdot 12H_2O$ (0.11 g, 0.325 mmol) in MeOH (10 mL) is added dropwise the ketoester **4c** or **4d** (2.6 mmol) with ice cooling and stirring, and the mixture is stirring for 5 h at room temperature. Then, a 10% aqueous solution of NaOH (10 mL) is added and stirring is continued for 1 h at room temperature. The mixture is acidified to pH 1–2 with conc. hydrochloric acid, stirring for 1 h at 0°C, then extracted with Et_2O (3 × 15 mL), dried ($MgSO_4$), and evaporated to give the lactone **5** (at least 90% pure by GLC). Further purification by chromatography over silica gel (0.063–0.200 mm) using EtOAc/hexane (3:7) as eluent, affords the 100% pure lactone **5**.

4-Nonanolide (**5c**); yield: 0.34 g (85%); b.p. 190°C (bath)/10 Torr (kugelrohr).

$C_9H_{16}O_2$	calc.	C 69.19	H 10.32
(156.2)	found	69.30	10.11

IR (neat): $\nu = 1770$ (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 0.9$ (t, 3H, J = 6 Hz); 1.05–2.15 (m, 10H); 2.20–2.70 (m, 2H); 4.30–4.70 (m, 1H).

4-Phenyl-4-butanolide (**5d**); yield: 0.252 g (60%); b.p. 115°C/0.6 Torr (Lit.[22], b.p. 171–172°C/11 Torr)

$C_{10}H_{10}O_2$	calc.	C 74.05	H 6.22
(162.2)	found	74.15	6.40

IR (neat): $\nu = 1770$ (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$): $\delta = 1.85$–2.88 (m, 4H); 5.2–5.65 (m, 1H); 7.1–7.6 (m, 5H).

The authors thank Ministero della Pubblica Istruzione (M.P.I.) of Italy for financial support.

Received: 13 January 1987

(1) Seebach, D., Colvin, E.W., Leher, F., Weller, T. *Chimia* **1979**, *33*, 1.
(2) Pollini, G.P., Barco, A., DeGiuli, G. *Synthesis* **1972**, 44.
(3) Bakuzis, P., Bakuzis, M.L., Weingartner, T.F. *Tetrahedron Lett.* **1978**, 2371.
(4) Miller, D.D., Moorthy, K.B., Hamada, A. *Tetrahedron Lett.* **1983**, *24*, 555.
(5) Stevens, R.V., Lee, A.W.M. *J. Chem. Soc. Chem. Commun.* **1982**, 102.
(6) Clark, J.H., Cork, D.G. *J. Chem. Soc. Chem. Commun.* **1982**, 635.
(7) Clark, J.H., Cork, D.G. *Chem. Lett.* **1983**, 1145.
(8) Nakashita, Y., Hesse, M. *Helv. Chim. Acta* **1983**, 845.
(9) McMurry, J.E., Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.
(10) Miyakoshi, T., Saito, S. *Yakugaku* **1982**, *31*, 35; *C. A.* **1982**, *96*, 142217.
(11) Miyakoshi, T., Saito, S. *Yakugaku* **1982**, *31*, 231; *C. A.* **1982**, *97*, 38526.
(12) Miyakoshi, T., Saito, S. *Yakugaku* **1982**, *31*, 749; *C. A.* **1982**, *97*, 6536.
(13) Ono, N., Miyake, H., Kaji, H. *J. Chem. Soc. Chem. Commun.* **1983**, 875.
(14) Ono, N., Kamimura, A., Kaji, A. *Synthesis* **1984**, 226.
(15) Rosini, G., Marotta, E., Ballini, R., Petrini, M. *Synthesis* **1986**, 237.
(16) Ballini, R., Petrini, M. *Synthesis* **1986**, 1024.
(17) See for example: Miyashita, M., Kumazawa, T., Yoshikoshi, A. *Chem. Lett.* **1980**, 1043.
Patterson, J.W., McMurry, T.E. *Chem. Commun.* **1971**, 488.
Naoshima, Y., Ozawa, H., Kondo, H., Hayashi, S. *Agric. Biol. Chem.* **1983**, *47*, 1431.
(18) We previously reported the utilization of Amberlyst-A21 in nitroaldol reactions: Rosini, G., Ballini, R., Petrini, M., Sorrenti, P. *Tetrahedron* **1984**, *40*, 3809.
(19) Chasar, D.W. *Synthesis* **1982**, 841; and references cited therein.
(20) Huggenberg, W., Hesse, M. *Helv. Chim. Acta* **1983**, *66*, 1519.
Kienzle, F., Holland, G.W., Kwoh, S., Rosen, P. *J. Org. Chem.* **1973**, *38*, 3440.
Ballini, R., Petrini, M., Marotta, E. *Synth. Commun.* **1987**, in press.
(21) Nagarajan, A., Porchezhiyan, V., Balasubramanian *Indian J. Chem. Sect. B* **1985**, *24*, 1202.
(22) Cromwell, N.H., Creger, P.L., Cook, K.E. *J. Am. Chem. Soc.* **1956**, *78*, 4412.